PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference 533739	Date of mailing *(day/month/year)* **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/015773	19.10.2004	21.10.2003

International Patent Classification (IPC) or both national classification and IPC

Applicant

Dainippon Sumitomo Pharma Co., Ltd.

1 This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis* 1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2 FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3 For further details, see notes to Form PCT/ISA/220

Name and mailing address of the ISA/JP	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/015773

Box No. I Basis of this opinion

1 With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2 With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b format of material

☐ in written format

☐ in computer readable form

c time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4 Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/JP2004/015773

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 27

because:

☒ the said international application, or the said claims Nos. 27
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claim 27 relates to methods for treatment of the human body by therapy.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed

☒ no international search report has been established for said claims Nos. 27

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/015773

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 2, 9, 14, 15, 25, 26, 28	YES
	Claims	3-8, 10-13, 16-24	NO
Inventive step (IS)	Claims	1, 2, 9, 14, 15, 25, 26, 28	YES
	Claims	3-8, 10-13, 16-24	NO
Industrial applicability (IA)	Claims	1-26, 28	YES
	Claims		NO

2. Citations and explanations:

(Documents cited in the ISR)

Document 1: WO 2002/014280 A1 (Ono Pharmaceutical Co., Ltd.) 21 February 2002
Document 2: JP 2003-505420 A (Schering Corporation) 12 February 2003
Document 3: JP 2002-521472 A (Schering Corporation) 16 July 2002
Document 4: US 4795757 A (Rorer Pharmaceutical Corporation) 03 January 1989
Document 5: US 3759974 A (Knoll A.G. Chemische Fabriken) 18 September 1973
Document 6: Chemical & Pharmaceutical Bulletin, 1977, Vol. 25, No.4, p. 775-83
Document 7: Journal of Medicinal Chemistry, 1991, Vol. 34, No.7, p. 2219-25
Document 8: Biochemical Pharmacology, 1995, Vol. 50, No.4, p.451-7
Document 9: JP 7-508263 A (SmithKline Beechham Corporation) 14 September 1995
Document 10: JP 6-25213 A (Recordati S.A.Chemical and Pharmaceutical Company) 01 February 1994
Document 11: US 3979444 A (The Upjohn Company) 07 September 1976
Document 12: DE 2109155 A1 (C. H. Boehringer Sohn) 14 September 1972
Document 13: DE 752755 C2 (I. G. Farbenindustrie A.G.) 10 November 1952
Document 14: US 3970656 A (Government of the United States) 20 July 1976
Document 15: GB 948874 A (Dr. KARL THOMAE G.M.B.H.) 05 February 1964
Document 16: US 3627772 A (Boehringer Ingelheim GmbH) 14 December 1971
Document 17: FR 1316888 A (C.H.Borhringer Sohn.) 26 April 1963
Document 18: JP 50-5197 B1 (John Wyeth and Brother Limited) 28 February 1975
Document 19: CH 277304 B (Rathgeb Fritz) 16 November 1951
Document 20: GB 591992 A (SOCIETY OF CHEMICAL INDUSTRY IN BASLE) 04 September 1947
Document 21: US 2486792 A (Ciba Pharmaceutical Products, Incorporated) 01 November 1949
Document 22: US 2551152 A (Ciba Pharmaceutical Products, Inc.) 01 May 1951
Document 23: WO 2003/053361 A2 (OSI PHARMACEUTICALS, INC.) 03 July 2003
Document 24: Bioorganic & Medicinal Chemistry Letters, 1997, Vol. 7, No. 19, p. 2531-6
Document 25: JP 9-500361 A (Merrell Dow Pharmaceuticals Incorporated) 14 January 1997
Document 26: JP 2002-524445 A (Pfizer Products Inc.) 06 August 2002
Document 27: Journal of Heterocyclic Chemistry, 1983, Vol. 20, p.771-2

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/JP2004/015773

Box No. VI Certain documents cited

1. Certain published documents (Rule 43*bis*.1 and 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 2004/096801 A1 [E, X]	11.11.2004	20.04.2004	23.04.2003
WO 2004/056771 A1 [E, X]	08.07.2004	18.12.2003	20.12.2002
WO 2004/020411 A1 [E, X]	11.03.2004	26.08.2003	29.08.2002
WO 2003/091216 A1 [E, X]	06.11.2003	22.04.2003	25.04.2002

2. Non-written disclosures (Rule 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/015773

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The claims related to the inventions of claims 1-26 and 28 are ambiguous in the description of "prodrug" in claims 1-26 and 28.

Claims 1-26 and 28 relate to a compound represented by formula (I) or formula (I') or a pharmaceutical agent that contains this compound as an active ingredient, but only an extremely small part of the claimed compounds are disclosed in the sense of PCT Article 5.

Consequently, claims 1-26 and 28 are not adequately supported by the description in the sense of PCT Article 6.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

(Claims 1, 2, 9, 14, 15, 25, 26, and 28)

The inventions described in claims 1, 2, 9, 14, 15, 25, 26, and 28 are not described in the documents cited in the ISR nor are they easily conceived of by any of the descriptions of any of these documents.

Consequently, the inventions described in claims 1, 2, 9, 14, 15, 25, 26, and 28 appear to possess novelty and involve an inventive step.

(Claims 3-8, 10-13, and 16-24)

(1) Document 1 describes compounds of the general formula (I) and therapeutic agents thereof. Thus, the inventions in claims 3, 5, and 21-24 does not appear to possess novelty or involve an inventive step based on documents 1.

(2) Documents 2 and 3 describe biphenyl piperidine derivatives and therapeutic agents thereof.

Thus, the inventions in claims 3-5 and 21-24 do not appear to possess novelty or involve an inventive step based on documents 2 and 3.

(3) Document 4 describes compounds represented by (II) and therapeutic agents thereof, and document 5 describes compounds represented by (I) and therapeutic agents thereof.

Thus, the inventions in claims 3-5, 10, 11, and 17-24 does not appear to possess novelty or involve an inventive step based on documents 4 and 5.

Documents 4 and 5 do not describe that 2 cyclohexane ring substituents are in the trans position, but selecting trans compounds wherein only one isomer is present from a cis-trans mixture could be easily conceived of by a person skilled in the art.

Thus, the inventions in claims 12 and 13 does not appear to possess novelty or involve an inventive step based on documents 4 do not appear to involve an inventive step based on documents 4 and 5.

(4) Document 6 describes compound IV, document 7 describes compound 18b, and document 8 describes compound (1).

Thus, the inventions in claims 3-5, 10-13, and 17-20, 22, and 23 does not appear to possess novelty or involve an inventive step based on documents 6-8, nor does the invention in claim 21 based on documents 7 and 8.

(5) Document 9 describes compounds represented by formula (I) and therapeutic compositions thereof, and document 10 describes amines represented by "Chem. 6."

Thus, the inventions in claims 3-5, 10, 17-23 does not appear to possess novelty or involve an inventive step based on documents 9 and 10, nor does the invention in claim 24 based on document 9.

(6) Document 11 describes compounds represented by formula (I) and pharmaceutical agents thereof.

Thus, the inventions in claims 3-5, 10, 16-20, and 22-24 are inventions described in document 11.

(7) Document 12 describes (I) compounds and pharmaceutical agents thereof, and documents 13-15 describe alkanoyl piperidine derivatives and pharmaceutical agents thereof.

Thus, the inventions in claims 3, 5, and 22-24 does not appear to possess novelty or involve an inventive step based on documents 12-15.

(8) Documents 16 and 17 describe alkanoyl piperidine derivatives or pharmaceutical agents thereof and 4-cyanopiperidine as an intermediate and document 18 describes azepane derivatives and pharmaceutical agents thereof.

Thus, the inventions in claims 3, 5, and 21-24 does not appear to possess novelty or involve an inventive step based on documents 16-18.

(9) Documents 19-25 describe compounds that are 4-allylpiperidine-4-carboxylic nitrile.

Thus, the inventions in claims 3, 5, and 21-23 does not appear to possess novelty or involve an inventive step based on documents 19-25.

(10) Document 26 describes 2- pyrimidyl piperazine derivatives and therapeutic compositions thereof.

Thus, the inventions in claims 3, 5-8, and 22-24 do not appear to possess novelty or involve an inventive step based on document 26.

(11) Document 27 describes 4-cyano-4-phenylpiperidine derivatives.

Thus, the inventions in claims 3, 5, and 21-23 does not appear to possess novelty or

Supplemental Box

involve an inventive step based on document 27.

(Continuation of International Patent Classification (IPC)

Int.Cl[7] A61K31/417, 31/4164, 31/4196, C07C311/20, 311/07, 255/46, 311/39, 311/21, 229/48, 217/52, 311/05, 311/18, 233/05, 233/78, 237/24, 323/36, 317/32, 309/46, C07D207/38, 209/04, 211/14, 239/42, 401/04, 401/14, 403/06, 413/04, 417/04, 409/04, 263/58, 277/82, 541/02, 333/20, 321/38, 233/88, 213/36, 513/04, 295/22, 295/14, 215/38, 249/08, 307/79, 307/82, 223/06, 223/04, 317/58, A61P3/06, 9/00, 9/10, 7/02, 43/00